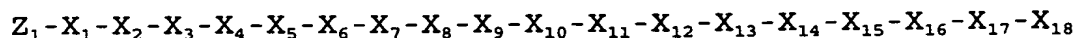


What Is Claimed Is:

1. An ApoA-I agonist comprising:

(i) a 14 to 22-residue peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises the structural formula (I):



X_1 is Pro (P), Ala (A), Gly (G), Asn (N), Gln (Q) or D-Pro (p);

X_2 is an aliphatic amino acid;

X_3 is Leu (L);

X_4 is an acidic amino acid;

X_5 is Leu (L) or Phe (F);

X_6 is Leu (L) or Phe (F);

X_7 is a basic amino acid;

X_8 is an acidic amino acid;

X_9 is Leu (L) or Trp (W);

X_{10} is Leu (L) or Trp (W);

X_{11} is an acidic amino acid or Asn (N);

X_{12} is an acidic amino acid;

X_{13} is Leu (L), Trp (W) or Phe (F);

X_{14} is a basic amino acid or Leu (L);

X_{15} is Gln (Q) or Asn (N);

X_{16} is a basic amino acid;

X_{17} is Leu (L);

X_{18} is a basic amino acid;

Z_1 is H_2N- or $RC(O)NH-$;

Z_2 is $-C(O)NRR$, $-C(O)OR$ or $-C(O)OH$ or a salt thereof;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 4-residue peptide or peptide analogue;

each " - " between residues X_n independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

5 (ii) a deleted form of structural formula (I) in which at least one and up to eight of residues $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}$ and X_{18} are deleted; or

10 (iii) an altered form of structural formula (I) in which at least one of residues $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}$ or X_{18} is conservatively substituted with another residue.

15 2. The ApoA-I agonist of Claim 1 which exhibits at least about 38% LCAT-activation activity as compared with human ApoA-I.

20 3. The ApoA-I agonist of Claim 1 which is the altered form of structural formula (I).

4. The ApoA-I agonist of Claim 3 in which the hydrophobic residues are fixed according to structural formula (I) and at least one non-fixed residue is conservatively substituted with another residue.

25 5. The ApoA-I agonist of Claim 4 in which:
 X_1 is Pro (P), D-Pro (p), Gly (G), Asn (N) or Ala (A);

X_2 is Ala (A), Leu (L) or Val (V);

30 X_3 is Leu (L);

X_5 is Leu (L) or Phe (F);

X_6 is Leu (L) or Phe (F);

X_9 is Leu (L) or Trp (W);

X_{10} is Leu (L) or Trp (W);

35 X_{13} is Leu (L), Trp (W) or Phe (F);

X_{17} is Leu (L); and

at least one of X₄, X₇, X₈, X₁₁, X₁₂, X₁₄, X₁₅, X₁₆ and X₁₈ is conservatively substituted with another residue.

6. The ApoA-I agonist of Claim 3 in which the hydrophilic residues are fixed according to structural formula (I) and at least one non-fixed residue is conservatively substituted with another residue.

7. The ApoA-I agonist of Claim 6 in which:

X₄ is Asp (D) or Glu (E);
X₇ is Arg (R), Lys (K) or Orn;
X₈ is Asp (D) or Glu (E);
X₁₁ is Asn (N) or Glu (E);
X₁₂ is Glu (E);
X₁₄ is Lys (K), Arg (R) or Orn;
X₁₅ is Gln (Q) or Asn (N);
X₁₆ is Lys (K), Arg (R) or Orn;
X₁₈ is Asn (N) or Gln (Q); and

at least one of X₁, X₂, X₃, X₅, X₆, X₉, X₁₀, X₁₃ and X₁₇ is conservatively substituted with another residue.

8. The ApoA-I agonist of Claim 6 in which X₃ is Leu (L), X₆ is Phe (F), X₉ is Leu (L) or Trp (W), X₁₀ is Leu (L) or Trp (W) and at least one of X₁, X₂, X₅, X₁₃ and X₁₇ is conservatively substituted with another residue.

9. The ApoA-I agonist of Claim 5 or 7 in which the substituting residue is classified within the same subcategory as the substituted residue.

10. The ApoA-I agonist of Claim 1 which is the deleted form of structural formula (I).

11. The ApoA-I agonist of Claim 10 in which one helical turn of the peptide or peptide analogue is deleted.

12. The ApoA-I agonist of Claim 1 which is an 18-residue peptide or peptide analogue of structural formula (I).

13. The ApoA-I agonist of Claim 12 in which:
the "-" between residues designates -C(O)NH-;
Z₁ is H₂N-; and
Z₂ is -C(O)OH or a salt thereof.

14. The ApoA-I agonist of Claim 13, in which:
X₁ is Pro (P), Ala (A), Gly (G), Asn (N) or D-Pro
(p);

X₂ is Ala (A), Val (V) or Leu (L);
X₃ is Leu (L);
X₄ is Asp (D) or Glu (E);
X₅ is Leu (L) or Phe (F);
X₆ is Leu (L) or Phe (F);
X₇ is Arg (R), Lys (K) or Orn;
X₈ is Asp (D) or Glu (E);
X₉ is Leu (L) or Trp (W);
X₁₀ is Leu (L) or Trp (W);
X₁₁ is Glu (E) or Asn (N);
X₁₂ is Glu (E);
X₁₃ is Leu (L), Trp (W) or Phe (F);
X₁₄ is Arg (R), Lys (K) or Orn;
X₁₅ is Gln (Q) or Asn (N);
X₁₆ is Arg (R), Lys (K) or Orn;
X₁₇ is Leu (L); and
X₁₈ is Arg (R), Lys (K) or Orn.

15. The ApoA-I agonist of Claim 1 which is selected from the group consisting of:

peptide 191 PVLDLLRELLEELKQK* (SEQ ID NO:191);
peptide 192 PVLDFKELLEELKQK* (SEQ ID NO:192);
peptide 193 PVLDFRELLEELKQK* (SEQ ID NO:193);
peptide 194 PVLELFRELLEELKQK* (SEQ ID NO:194);

peptide 195 PVLELFKELLEELKQKLK* (SEQ ID NO:195);
 peptide 196 PVLDLFRELLEELKNKLK* (SEQ ID NO:196);
 peptide 197 PLLDLFRELLEELKQKLK* (SEQ ID NO:197);
 peptide 198 GVLDLFRELLEELKQKLK* (SEQ ID NO:198);
 5 peptide 199 PVLDLFRELWEELKQKLK* (SEQ ID NO:199);
 peptide 200 NVLDLFRELLEELKQKLK* (SEQ ID NO:200);
 peptide 201 PLLDLFKELLEELKQKLK* (SEQ ID NO:201);
 peptide 202 PALELFKDLLEELRQKLR* (SEQ ID NO:202);
 peptide 203 AVLDLFRELLEELKQKLK* (SEQ ID NO:203);
 10 peptide 204 PVLDFFRELLEELKQKLK* (SEQ ID NO:204);
 peptide 205 PVLDLFREWLEELKQKLK* (SEQ ID NO:205);
 peptide 206 PLLELLKELLEELKQKLK* (SEQ ID NO:206);
 peptide 207 PVLELLKELLEELKQKLK* (SEQ ID NO:207);
 peptide 208 PALELFKDLLEELRQRLK* (SEQ ID NO:208);
 15 peptide 209 PVLDLFRELLNELLOQKLK (SEQ ID NO:209);
 peptide 210 PVLDLFRELLEELKQKLK (SEQ ID NO:210);
 peptide 211 PVLDLFRELLEELOQOLO* (SEQ ID NO:211);
 peptide 212 PVLDLFOELLEELOQOLK* (SEQ ID NO:212);
 peptide 213 PALELFKDLLEEFRQRLK* (SEQ ID NO:213);
 20 peptide 214 pVLDLFRELLEELKQKLK* (SEQ ID NO:214);
 peptide 215 PVLDLFRELLEEWKQKLK* (SEQ ID NO:215);
 peptide 229 PVLELLEERLLEDLQKKLK (SEQ ID NO:229);
 peptide 230 PVLDLFRELLEKLEQKLK (SEQ ID NO:230);
 25 peptide 231 PLLELFKELLEELKQKLK* (SEQ ID NO:231);

in either the N- and/or C-terminal blocked or unblocked forms.

16. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

each "HH" is independently a peptide or peptide

5 analogue according to Claim 1;

each "LL" is independently a bifunctional linker;

and

each " - " independently designates a covalent linkage.

10

17. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (III):

15 (III) $X-N_{y_a}-X_{(y_a-1)}-(N_{y_b}-X_{(y_b-1)})_p$

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $HH-(LL_m-HH)_nLL_m-HH$;

each HH is independently a core peptide of structure

20 (I) or an analogue or mutated, truncated, internally deleted or extended form thereof as described herein;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

25 N_{y_a} and N_{y_b} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{y_a} and N_{y_b} , respectively;

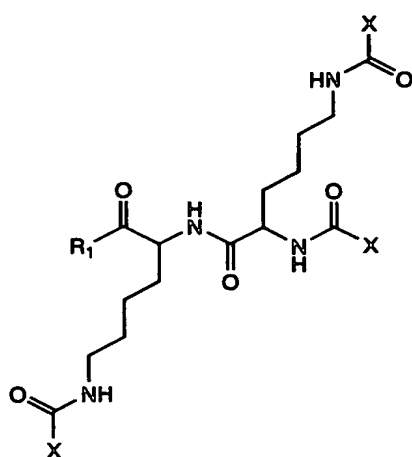
each y_a or y_b is independently an integer from 3 to 8;

30 p is an integer from 0 to 7; and

each "-" independently designates a covalent bond.

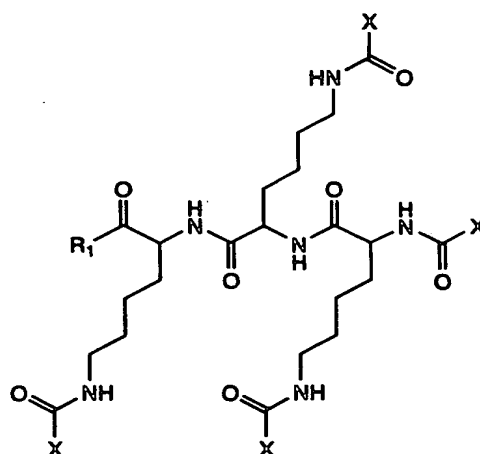
18. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (IV) or (V):

35



(IV)

-OR-



(V)

or a pharmaceutically acceptable salt thereof, wherein:
 each X is independently $\text{HH}(\text{LL}_m\text{--HH})_n\text{LL}_m\text{--HH}$;
 5 each HH is independently a peptide or peptide
 analogue according to Claim 1;
 each LL is independently a bifunctional linker;
 each n is independently an integer from 0 to 1;
 each m is independently an integer from 0 to 8;
 10 R_1 is -OR or -NRR; and
 each R is independently -H, $(\text{C}_1\text{--C}_6)$ alkyl, $(\text{C}_1\text{--C}_6)$
 alkenyl, $(\text{C}_1\text{--C}_6)$ alkynyl; $(\text{C}_5\text{--C}_{20})$ aryl $(\text{C}_6\text{--C}_{26})$ alkaryl, 5-20
 membered heteroaryl or 6-26 membered alkheteroaryl.

15 19. The multimeric ApoA-I agonist of Claim 16, 17 or 18
 in which the bifunctional linker is cleavable.

20 20. The ApoA-I multimeric agonist of Claim 16, 17 or 18
 in which n is 0.

21. The multimeric ApoA-I agonist of Claim 20 in which m is 0.

22. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 13.

23. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 14.

24. The multimeric ApoA-I agonist of Claim 16, 17 or 18 in which each HH is independently a peptide according to Claim 15.

25. An ApoA-I agonist-lipid complex comprising an ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist according to Claim 16, a multimeric ApoA-I agonist according to Claim 17, or a multimeric ApoA-I agonist according to Claim 18.

26. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 12.

27. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 13.

28. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 14.

29. The ApoA-I agonist-lipid complex of Claim 25 in which the ApoA-I agonist is a peptide according to Claim 15.

30. The ApoA-I agonist-lipid complex of Claim 25 in which the lipid is sphingomyelin.

31. The ApoA-I agonist-lipid complex of Claim 25 which is in the form of a lyophilized powder.

5 32. The ApoA-I agonist-lipid complex of Claim 25 which is in the form of a solution.

10 33. A pharmaceutical composition comprising an ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist according to Claim 16, a multimeric ApoA-I agonist according to Claim 17, or a multimeric ApoA-I agonist according to Claim 18.

15 34. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 12.

20 35. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 13.

36. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 14.

25 37. The pharmaceutical composition of Claim 33 in which the ApoA-I agonist is a peptide according to Claim 15.

30 38. The pharmaceutical composition of Claim 33, 34, 35, 36 or 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

35 39. The pharmaceutical composition of Claim 38 in which the ApoA-I agonist-lipid complex is in the form of a lyophilized powder.

40. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

41. The method of Claim 40 in which the ApoA-I agonist is in the form of a pharmaceutical composition, said composition comprising the ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent.

42. The method of Claim 40 in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

43. The method of Claim 40 in which the disorder associated with dyslipidemia is hypercholesterolemia.

44. The method of Claim 40 in which the disorder associated with dyslipidemia is cardiovascular disease.

45. The method of Claim 40 in which the disorder associated with dyslipidemia is atherosclerosis.

46. The method of Claim 40 in which the disorder associated with dyslipidemia is restenosis.

47. The method of Claim 40, in which the disorder associated with dyslipidemia is HDL or ApoA-I deficiency.

48. The method of Claim 40, in which the disorder associated with dyslipidemia is hypertriglyceridemia.

49. The method of Claim 40, in which the disorder associated with dyslipidemia is metabolic syndrome.

50. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

5 51. The method of Claim 40 or 50 in which said subject is a human.

10 52. The method of Claim 40 or 50 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.